**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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| Applicants: | Hostetler et al. | Art Unit: | 1612 |
| Application No.: | 10/770,885 | Examiner: | Snigdha Maewall |
| Filed: | February 2, 2004 | Confirmation No.: | 1066 |
| Title: | LIPID DRUG CONJUGATES FOR LOCAL THERAPY OF EYE DISEASES | | |

**DECLARATION OF KARL Y. HOSTETLER UNDER 37 C.F.R. §1.132**

I, Karl Y. Hostetler, M.D., do hereby declare and state that:

1. I am Professor of Medicine at the University of California at San Diego (UCSD) School of Medicine. I am also a Director at the San Diego VA Medical Center Endocrinology Clinic; and am an Associate Member of the Rebecca and John Moores Cancer Center, UCSD. I received my M.D. from Western Reserve University School of Medicine in Cleveland, Ohio in 1965. I was an Investigator at the Marine Biological Laboratories in Woods Hole, Massachusetts from 1962-1964 and again in 1966-1968; a USPHS Postdoctoral Trainee in Medicine at Case Western Reserve University in 1966-1969; a Resident in the Department of Medicine University Hospitals of Cleveland in 1969; and a Special Fellow in Endocrinology and Metabolism at the Cleveland Clinic Foundation in 1969-1970. My complete *curriculum vitae* is attached as Exhibit A.

2. I am familiar with the contents of the above-identified patent application for which I am an inventor, and understand that the application includes claims to methods for treating eye diseases using certain compounds. I am familiar with the the methods and compounds that are claimed in the present application.

3. I have reviewed the Office Action mailed October 19, 2010, and I understand that claims 1, 7-12, 23-25, and 27 are rejected, *inter alia*, under 35 U.S.C. §103(a) as allegedly being obvious over Cheng (Investigative Ophthalmology & Visual

Science, May 2000, Vol. 41, No. 6). I would like to provide the following comments.

4. As discussed in the specification as filed, particularly in Example 5 at paragraph [0077], we showed that a single intravitreal injection of HDP-GCV (having a mean particle size of 8 to 43 μm) into rabbit eyes prevents HSV-1 infection of the retina for 20 weeks, whereas a single intravitreal injection of GCV provided less than one week of protection (see, Cheng et al. *Invest Ophthalmol Vis Sci.* 2002;43:515-21). In, the specification as filed, particularly in Example 3 at paragraph [0071] to [0072] and Figures 4a and 4b, we found that microfluidization of HDP-P-GCV to a particle size of about 4.4 μm, provides a faster release rate and higher free drug concentration in the upper vitreous (away from the injection site) than does the unmodified HDP-P-GCV, i.e. HDP-P-GCV having a mean particle size of 8 to 43 μm.

5. Further, the cited reference teaches liposomal formulations of HDP-P-GCV. As discussed on page 1531 and in Table 4 of Cheng, it was found that a single intravitreal injection of the liposomal formulation of HDP-P-GCV into rabbit eyes provided only a 4- to 6-week period of antiviral effect.

6. I submit that the 20 week length of duration of the antiviral effect using the microfluidized version of the compound and the finding that microfluidization to about 4.4 μm provides for a faster release rate and higher free drug concentration in the upper vitreous were unexpected based on the teachings in the cited Cheng reference. Further, there would be no reason given the teachings in Cheng to omit the delivery vehicle (liposomes).

7. I further declare that all statements made herein of knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine, or imprisonment, or both under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 2-16-11

Karl Hostetler

Karl Y. Hostetler, M.D.